REMARKS

In the Office Action dated October 6, 2006, claims 1-29 were examined with the result that claims 12, 20 and 21 were allowed, while claims 1-11, 13-19 and 22-29 were rejected. In response, Applicant has filed the present Amendment, and an exhibit attached to this Amendment comparing the biological activities of the presently claimed compounds of claims 13, 14, 15 and 16 with those disclosed in U.S. Patent 6,806,262 and WO 01/92221, the primary references utilized by the Examiner to reject the claims. Applicant also previously submitted a Glebocka et al article recently published in the Journal of Medical Chemistry, Vol. 49, pages 2909-2920 (2006) containing biological data as well as a discussion concerning the compounds of claims 13, 14, 15 and 16. In view of the enclosed exhibit, Glebocka et al article and the following remarks, reconsideration of this application is requested.

In the current Office Action, the Examiner rejected claims 1-11, 13-19 and 22-29 under the Doctrine of Obviousness Type Double Patenting as being unpatentable over claims 5-7 and 33-56 of U.S. Patent 6,806,262. The Examiner indicated that although the conflicting claims are not identical, they are not patentable distinct from each other since the presently claimed compounds are obvious in view of the compounds disclosed in the '262 patent. Although none of the presently claimed compounds are specifically exemplified in the '262 patent, the Examiner indicated that it would be obvious to one skilled in the art to prepare additional beneficial compounds because the '262 patent teaches similar compounds for similar claimed uses.

In Applicant's previous response dated August 10, 2006, Applicant described for the Examiner the differences in biological activities of the presently claimed compounds from those disclosed in U.S. Patent Nos. 6,392,071 and 5,843,928. Those arguments were found persuasive, and the Examiner withdrew the rejections based on the '071 and '928 references. The Examiner, however, in the present Office Action, has once again rejected the claims, but this time basing the rejection on U.S. Patent 6,806,262 and its corresponding PCT International Application No. WO 01/92221.

In response, Applicant submits the enclosed exhibit which consists of a table comparing the compounds of claims 13, 14, 15 and 16 with the prior art compounds of the '262 and '221 references. The exhibit is believed to clearly illustrate the change of activity that occurs from untreated control upon administration of the compounds so that the Examiner can better understand the difference between "low," "moderate," and "high" activity. Applicant believes the enclosed table clearly illustrates the difference in the biological activities of the claimed vitamin D analogs versus the prior art compounds of the '262 and '221 references.

THE BIOLOGICAL ACTIVITIES OF THE CLAIMED VITAMIN D ANALOGS

Applicant believes it would not have been obvious to select the presently claimed compounds in view of the compounds covered by the '262 and '221 references because of the differences in the biological activities of the presently claimed compounds versus those described in the '262 and '221 references. More specifically, the biological activities of the presently claimed compounds can be found in the specification in Figures 5 and 6 which are described in paragraph 00163 on page 58 of the specification as filed. As stated therein:

> "Figures 5 and 6 show a comparison of the calcemic activity of the known active 19-nor analog 2MD and the presently claimed F-Wit, 1AGR and 1AGS analogs. Figure 5 shows that F-Wit, 1AGR and 1AGS all have relatively high intestinal calcium transport activity, and are more active than 2MD in intestinal calcium transport activity. Also, Figure 6 shows that F-Wit, 1AGR and 1AGS all have significant ability to mobilize calcium from bone, and are less active in this regard than 2MD. Thus, in summary, the 2-propylidene-19-nor-analogs of structure I, and particularly F-Wit, 1AGR and 1AGS, show a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity and moderate bone calcium mobilization activity."

The compound referred to as "F-Wit" is the methoxymethoxy compound defined by claims 12, 20 and 21 which have been allowed by the Examiner. The compounds "1 AGR" and "1 AGS" refer to the E-isomers of the hydroxypropylidene and (20S)-

hydroxypropylidene compounds of claims 13 and 15, respectively. With regard to the Z-isomers, Applicant refers the Examiner to the Glebocka article at pages 2913 and 2914 where it is stated:

> "Another structure/activity pattern that has been reported before is that Z-isomers of 2-alkylidene vitamin D analogues have less activity than their counterparts in the E-configuration. This pattern was repeated with this series of compounds as well in that 7a and 7b were less active than 6a and 6b both in vitro and in vivo."

Thus, the presently claimed 2-propylidene-19-nor-analogs in the present patent application all have relatively high intestinal calcium transport activity. In addition, the claimed 2-propylidene-19-nor-analogs have significant (or what is termed "moderate" in the accompanying Exhibit A) bone calcium mobilization activity.

THE BIOLOGICAL ACTIVITIES OF THE PRIOR ART VITAMIN D ANALOGS IN US 6,806,262 AND WO 01/92221

The calcemic activities for the four 2-ethylidene compounds are set forth in U.S. Patent 6,806,262, particularly in Table 1 found at column 16 of the '262 patent. The '262 patent summarizes the calcemic activity of these four compounds beginning at column 15, line 58 and continuing through line 62 as follows:

> "Both E isomers of 2-ethylidene-19-nor-vitamins, when tested in vivo in rats (Table 1) exhibited very high calcemic activity, the (20S)-compound being especially potent. On the contrary, isomeric Z compounds are significantly less active."

As will be seen from the following discussion and the attached Exhibit A, it can be concluded from the data contained in Table 1 of the '262 patent that the 2-ethylidene compounds have "moderate" to "low" intestinal calcium transport activity, and also have very "low" bone calcium mobilization activity at the doses tested (with the exception of the (20S) E-isomer compound 4b which has high bone calcium mobilization activity).

SUMMARY

Exhibit A is a chart which summarizes and compares the biological activities of the four 2-ethylidene compounds as taught in the prior art '262 reference with the presently claimed hydroxypropylidene 19-nor-vitamin D compounds. Exhibit A illustrates the change of activity that occurs upon administration of 17 and/or 52 pmols of the two claimed E-isomer compounds versus the change of activity that occurs upon administration of 130 pmols of the four 2-ethylidene compounds. With regard to the Z-isomers claimed, the chart of Exhibit A refers to pages 2913 and 2914 of the Glebocka et al article which states that the activities of these two compounds were less than the E-isomers. Unfortunately, however, the actual data was not reported for the Z-isomers.

A comparison of the 2-ethylidene analogs disclosed in the '262 patent and the hydroxypropylidene compounds of claims 13-16 in the present patent application shows that there are significant differences in the calcemic activities of these compounds. The four 2-ethylidene analogs in the '262 patent have "moderate" to "low" intestinal calcium transport activity and extremely "low" bone calcium mobilization activity, with the exception of compound 4b. The Examiner should note, however, that prior art compound 4b was administered at 130 pmol whereas the hydroxypropylidene compounds were administered at only 52 pmol, i.e. an almost 3-fold higher dosage. In contrast, the presently claimed hydroxypropylidene compounds of claims 13-16 all have "high" intestinal calcium transport activity, and as shown in Exhibit A by the larger delta ("Δ") numbers, are clearly more active than any of the four 2-ethylidene analogs of the '262 reference in intestinal calcium transport activity. In addition, the presently claimed hydroxypropylidene compounds, although having "moderate" ability to mobilize calcium from bone are much more active in this regard than any of compounds 4a, 5a or 5b of the '262 reference.

Thus, the presently claimed hydroxypropylidene compounds have significantly different calcium transport activity as well as bone calcium mobilization activity than the 2-ethylidene analogs disclosed in the '262 patent. Clearly, such activities would not be

predicted based upon the structural similarity of the compounds. One skilled in the art would have predicted that the compounds should have approximately the same intestinal calcium transport activity and bone calcium mobilization activity due to their structural similarity, but instead, it is clear that the presently claimed hydroxypropylidene compounds have much higher intestinal calcium transport activity and higher bone calcium mobilization activity (other than compound 4b) than the 2-methylene analogs disclosed in the '262 patent. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-ethylidene analogs disclosed in the '262 patent.

Accordingly, Applicant believes the Examiner should withdraw the obviousness type double patenting rejection based on the 2-ethylidene analogs disclosed in the '262 patent, and the obviousness rejection under 35 USC §103(a) based on WO 01/92221.

There are advantages to using compounds with high intestinal calcium transport activity. For example, inflammatory bowel disease (IBD) is a disease of the intestine and thus a compound having high intestinal activity, as opposed to bone activity, would appear desirable. Also, in patients with resectioned bowels, one desires to maximize activity in that patient's shorter intestinal route.

Thus, Applicant believes it has compared the biological activities of the presently claimed compounds to the closest and most structurally similar compounds disclosed in the '262 and '221 references. As previously noted herein, the presently claimed hydroxypropylidene compounds have significantly different calcium transport and bone calcium mobilization activities than the 2-ethylidene analogs. Clearly, such activities would not have been predicted based upon the structural similarity of these compounds. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-ethylidene analogs taught in the '262 and '221 references.

Accordingly, Applicant believes the Examiner should withdraw the rejections based upon the '262 and '21 references.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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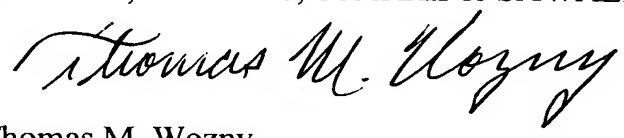

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EXHIBIT A

10/821,479 Application Compound	Compound No. in Glebocka et al article	Compound No. in US 6,806,262	Intestinal Calcium Transport Activity*	Bone Calcium Mobilization Activity**
2-(3'-hydroxypropylidene)-19-nor-1α,25-dihydroxyvitamin D_3 (E-isomer) (1AGR) Claim 13	6a		High Δ 7.0 @ 17 pmol (11.7-4.7) (Fig. 5)	Moderate Δ 4.6 @ 52 pmol (8.8-4.2) (Fig. 6)
2-(3'-hydroxypropylidene)-19-nor-1α,25-dihydroxyvitamin D_3 (Z-isomer) Claim 14	7a		Less than 1AGR (the E-isomer) (See the Glebocka et al article pp. 2913 and 2914)	Less than 1AGR (the E-isomer) (See the Glebocka et al article pp. 2913 and 2914)
2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 (E-isomer) (1AGS) Claim 15	6b		High Δ 5.3 @ 17 pmol (10.0-4.7) (Fig. 5)	Moderate Δ 3.7 @ 52 pmol (7.9-4.2) (Fig. 6)
2-(3'-hydroxypropylidene)-19-nor-(20S)-1α,25-dihydroxyvitamin D_3 (Z-isomer) Claim 16	7b		Less than 1AGS (the E-isomer) (See the Glebocka et al article pp. 2913 and 2914)	Less than 1AGS (the E-isomer) (See the Glebocka et al article pp. 2913 and 2914)
2-ethylidene-19-nor-1α,25-dihydroxyvitamin D_3 (E-isomer) U.S. 6,806,262		4a	Moderate ≈Δ 3.8 @ 130 pmol (6.8 ± 0.4 minus 3.0 ± 0.7)	Low ≈Δ 0.9 @ 130 pmol (5.2 ± 0.2 minus 4.3 ± 0.1)
2-ethylidene-19-nor-1α,25-dihydroxyvitamin D_3 (Z-isomer) U.S. 6,806,262		5a	Moderate ≈Δ 2.7 @ 130 pmol (5.7 ± 0.9 minus 3.0 ± 0.7)	Low ≈Δ 0.0 @ 130 pmol (4.2 ± 0.0 minus 4.3 ± 0.1)
(20S)-2-ethylidene-19-nor-1α,25-dihydroxyvitamin D_3 (E-isomer) U.S. 6,806,262		4b	Low ≈Δ 1.4 @ 130 pmol (5.8 ± 0.3 minus 4.4 ± 0.2)	High ≈Δ 8.0 @ 130 pmol (12.1 ± 0.6 minus 4.1 ± 0.2)
(20S)-2-ethylidene-19-nor-1α,25-dihydroxyvitamin D_3 (Z-isomer) U.S. 6,806,262		5b	Low ≈Δ 0.0 @ 130 pmol (3.8 ± 0.3 minus 4.4 ± 0.2)	Low ≈Δ 0.0 @ 130 pmol (4.0 ± 0.1 minus 4.1 ± 0.2)

*Data given as the increase in serosal/mucosal calcium above untreated control

**Data given as the increase in serum calcium above untreated control of rats on a 0.02% calcium diet